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Nuclear Medicine Program Progress Report for Quarter Ending March 31, 1993

F. F. Knapp, Jr. Group Leader

K. R. Ambrose
A. L. Beets
A. P. Callahan
D. W. McPherson
S. Mirzadeh
C. R. Lambert

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SUMMARY

As described earlier in ORNL/TM-12110 we have explored the possibility of measuring urinary radioactivity as an index of pancreatic lipase activity in rats after oral administration of a new triglyceride containing a radioactive iodine-125-labeled fatty acid moiety. The new agent, 1,2-dipalmitoyl-3[15-(p-iodophenyl)pentandecan-1-oyl]-rac-glycerol (1,2-Pal-3-IPPA), was prepared by the thallation-iodide displacement method. Following oral gavage of the radioiodinated triglyceride to rats, a significant portion of the administered activity was excreted in 24 hours in the urine (30.31 + 4.32%). More recently in normal human controls, similar results with high urinary excretion (76 ± 13.8% at 24 hrs.) were observed (ORNL/TM-12159).

In this report, we describe an evaluation of the metabolites excreted in the urine and the chemical species stored in adipose from rats. The urine activity co-chromatographed with hippuric acid by TLC indicating conjugation of the IPPA metabolites. Release of the acidic components from the conjugated excretory products by acid hydrolysis of the urine provided the radioactive acidic IPPA metabolites. Analysis of the Folch extracts of fat samples from rats demonstrated that the radioactive components co-chromatographed in the triglyceride region. Recent studies in patients with compromised pancreatic exocrine function conducted by collaborators at the Clinic for Nuclear Medicine in Bonn, Germany (J. Kropp, M.D. and H.-J. Biersack, M.D.) have demonstrated significantly decreased 24 hr. urinary excretion (26.30% ± 15.7%) compared with controls (76% ± 13.8%) following oral administration of [1-131]-1,2-Pal-3-IPPA. Thus, urine analysis after oral administration of [1-131]-1,2-Pal-3-IPPA may be a simple, non-invasive tool for the clinical evaluation of various diseases involving dietary fat digestion.

Also described in this report is a summary of recent measurements of the production yield of radioisotopes of medical interest in the hydraulic tube positions of the ORNL High Flux Isotope Reactor (HFIR). Also during this period, samples of the [I-131]-labeled racemic "IQNP" muscarinic-cholinergic receptor antagonist were supplied through a collaborative program with the Brookhaven National Laboratory (P. Som, D.V.M.) for high resolution autoradiographic studies in rat tissues. The first large-scale (0.5 Ci) tungsten-188/rhenium-188 generator was provided for collaborative studies for radiolabeling antibodies for patient tumor therapy with the University of New Jersey School of Medicine and Dentistry (D. Goldenberg, M.D., et al.).

FURTHER STUDIES WITH THE NEW RADIOIODINATED TRIGLYCERIDE TO EVALUATE PANCREATIC DISEASE - RESULTS IN PATIENTS WITH COMPROMISED PANCREATIC EXOCRINE FUNCTION

An accurate evaluation of fat adsorption can be an indirect measure of pancreatic lipase activity which is an important indicator for the diagnosis of many types of gastrointestinal disease. Traditional techniques to evaluate steatorrhea are often unpleasant or impractical and involve chemical fecal fat analysis and the evaluation of blood and fecal levels of radioactivity after administration of radioiodinated fats (e.g. "triolein"). We have prepared a new triglyceride agent containing radioiodinated 15-(p-iodophenyl)pentadecanoic acid (IPPA), in which the iodide is stabilized by attachment to the para-position of the terminal phenyl ring (ORNL/TM-12110 and -12159). Our approach is based on the expected urinary excretion of conjugated radioactive short-chain acid catabolites formed by β-oxidation of the radioiodinated IPPA released from the triglyceride by tissue lipase hydrolysis. Use of a triglyceride containing radioiodinated IPPA would thus be expected to overcome the problems encountered with the triolein approach. With an IPPA-labeled triglyceride, free radioiodide would not be expected to be formed, the agent would be stable for long-term storage, and IPPA, the expected metabolite released via hydrolysis has a well defined metabolic fate.

For the dual-label studies, [I-125]-1,2-Pal-3-IPPA and [I-131]-IPPA were combined and administered orally to rats. It was expected that the free [I-131]-IPPA would be directly absorbed with subsequent reesterification and further metabolism, etc., while [I-125]-IPPA must first be released from the triglyceride by hydrolysis prior to absorption and reesterification. Since the metabolism of both tracers is the same after adsorption, excretion results should thus be similar for both tracers. For animal studies, the female Fisher strain rats were fasted overnight. The radiolabeled triglyceride and IPPA were each dissolved in warm ethanol and an appropriate aliquot was added to 0.5 ml of Tween 20. The solution was warmed and the ethanol removed under a gentle argon stream. The Tween 20 solution was then diluted with 10 ml of saline to give a solution containing 1.1 μCi [I-125] and 2.4 μCi [I-131]. The [I-125]-1,2-Pal-3-IPPA/[I-131]-IPPA solution (0.5 ml) was then administered to metofane-anesthetized rats by oral gavage with a feeding needle. One group of four rats was housed in metabolism cages and allowed food and water *ad libitum*. The separated urine and feces were collected daily, aliquots counted,

and the daily and cumulative levels of [I-125] and [I-131] in the urine and feces then calculated (Table 1). Significantly more radioactivity was excreted in the urine compared to the feces.

Table 1. Distribution of Radioactivity in Urine and Feces From Rats Following Oral Administration of a [1-125]-1,2-Pal-3-IPPA/[1-131]-IPPA Mixture.

Iodine-125 (From 1,2-Pal-3-IPPA) and Iodine-131 (From [1-131]-IPPA)						
	Urine*		Feces*		Total**	
Days	[1-125]	[1-131]	[1-125]	[1-131]	[1-125]	[1-131]
1	30.31±4.32	35.0±7.29	8.00±1.69	4.54±1.27	38.31	39.54
2	4.97±0.56	4.87±0.68	1.34±0.23	0.59±0.16	44.62	45.00
3	2.97±0.48	3.16±0.60	0.45±0.11	0.17±0.06	48.04	48.33
4	2.14±0.36	2.40±0.46	0.31±0.10	0.13±0.07	50.49	50.86
5	1.22±0.06	1.42±0.08	0.16±0.04	0.09±0.04	51.87	52.37

* Mean values ±SD for five female Fisher rats. Each rat received a mixture of 1.1 μCi [I-125]-1,2-Pal-3-IPPA and 2.4 μCi [I-131]-IPPA in 0.5 ml of the formulation mixture by oral gavage with a feeding needle.

** Mean cumulative values.

Animals were also sacrificed at various time periods (n = 5 rats/group) and the distribution of the two radioisotopes then determined in the major organs, blood, thyroid and fat samples taken from the abdominal cavity (Table 2). The results demonstrate no significant accumulation of radioactivity in any of the tissues evaluated and low thyroid uptake, indicating low deiodination of both tracers. For evaluation of the radioactive components in the fat, the samples (0.98-2.27 gm) were homogenized in 10 ml of 2:1 $CHCl_3$:MeOH with a loose-fitting ground glass homogenizer. After addition of 0.5 ml of 10% H_2SO_4 and 2 mL of 0.29% saline solution, the samples were centrifuged, the lower organic layer separated, dried over anhydrous Na_2SO_4, and the solvent removed under a stream of argon. Samples were dissolved in $CHCl_3$ and aliquots applied to SiO_2 plates which were developed in $CHCl_3$. Aliquots of 24 hour urine samples were analyzed by TLC using a $CHCl_3$:HOAc (2:1) solvent system. Urine aliquots (0.1 ml) were also combined

in a reaction vial with 2 ml H_2SO_4, sealed and heated at 100°C for 30 min, cooled and extracted with $CHCl_3$. The upper organic layer was dried, and aliquots analyzed by TLC using 6% MeOH in $CHCl_3$. Urine samples and the chloroform extracts of aliquots hydrolyzed with H_2SO_4 were also analyzed by TLC (Table 3).

Table 2. Distribution of Radioactivity in Rat Tissues Following Administration of a [I-125]-1,2-Pal-3-IPPA/[I-131]-IPPA Mixture by Oral Gavage.*

Mean Per Cent Injected Dose/Gram						
Time After Administration						
Tissue	Radioisotope	4 hrs.	1 day	2 days	3 days	5 days
Blood	1-125	0.81±0.35	0.15±0.02	0.07±0.01	0.03±0.01	0.02±0.00
	1-131	0.86±0.39	0.08±0.02	0.04±0.01	0.02±0.00	0.02±0.00
Heart	1-125	0.89±0.37	0.30±0.05	0.20±0.09	0.21±0.13	0.06±0.01
	1-131	0.93±0.39	0.29±0.05	0.22±0.12	0.23±0.13	0.06±0.01
Kidneys	1-125	0.54±0.20	0.55±0.09	0.48±0.10	0.37±0.10	0.25±0.06
	1-131	0.51±0.20	0.53±0.11	0.49±0.11	0.40±0.12	0.28±0.08
Liver	1-125	1.34±0.61	0.48±0.05	0.13±0.02	0.06±0.00	0.04±0.01
	1-131	1.56±0.74	0.54±0.06	0.12±0.02	0.06±0.01	0.04±0.01
Stomach	1-125	4.74±1.10	0.21±0.09	0.15±0.05	0.08±0.02	0.08±0.04
	1-131	5.72±1.63	0.21±0.09	0.16±0.05	0.08±0.03	0.09±0.05
Thyroid**	1-125	0.24±0.11	0.36±0.11	0.36±0.05	0.38±0.11	0.23±0.02
	1-131	0.17±0.09	0.15±0.05	0.17±0.03	0.15±0.03	0.09±0.01
Fat***	1-125	0.60±0.32	2.24±0.77	2.35±0.52	2.35±0.58	1.84±0.41
	1-131	0.66±0.36	2.51±0.85	2.62±0.55	2.68±0.63	2.17±0.51

* Mean and ±SD for five female Fisher rats. Same rats described in Table 1.

** Thyroid data expressed as % dose/organ values.

*** White fat samples were taken from the abdominal cavity.

TLC analysis of the 24 hour urine demonstrated the presence of a major radioactive component with the mobility of authentic hippuric acid (R_f 0.55, $CHCl_3$:HOAc, 2:1; Table 3). The remainder of radioactivity on the TLC plates consisted of polar activity at the origin. The organic extracts of acid hydrolyzed urine samples were also analyzed by TLC and showed the presence of a major radioactive component chromatographing in the region of short chain free acids (R_f 0.35, 6% MeOH in $CHCl_3$). Fat samples were extracted by the Folch technique and the organic soluble products analyzed by TLC, demonstrating the presence of a radioactive component (Table 3) with the mobility of the triglyceride standard (R_f 0.55, 6% MeOH in $CHCl_3$). The remainder of the radioactivity on the plate was found at the origin and is expected to represent phospholipids.

Table 3. Results of Thin-layer Chromatographic Analysis of Folch Extracts of Fat Samples, Urine and Chloroform Extracts of Urine Acid Hydrolysates Following Oral Administration of a Mixture of [1-125]-1,2-Pal-3-IPPA and [1-131]-IPPA to Rats.#

Major Component			Mean % ±SD of Total on Plate	
Sample	Mobility, R_f	Solvent System	Iodine-125	Iodine-131
Fat Extract:				
4 Hours	0.55 *	$CHCl_3$	74.73 ± 4.44	76.48 ± 4.85
24 Hours	0.55 *	$CHCl_3$	92.21 ± 2.46	90.67 ± 2.64
24 Urine	0.45 **	$CHCl_3$:HOAc, 2:1	63.92 ± 3.48	77.56 ± 3.46
24 Urine Hydrolysate	0.55 ***	MeOH:$CHCl_3$, 6:94	66.43 ± 4.98	79.93 ± 2.92

Data represent the mean ±SD of the total applied to the TLC plates from samples from four rats. (Same rats described in Table 1.)

* Co-chromatographs with triglyceride standard.

** Co-chromatographs with hippuric acid standard.

*** Chromatographs in region of short-chain free acids.

In conjunction with collaborators at the Clinic for Nuclear Medicine at the University of Bonn, Germany, (J. Kropp, M.D. and H.-J. Biersack, M.D.), patients with established decreased pancreatic exocrine function have been recently evaluated. As described in ORNL/TM-12159, Dr. Kropp and colleagues had previously evaluated nine normal volunteers and eleven patients without signs of pancreatic disease. The 24 hr. urine excretion of activity was 76 ± 13.8% of the administered activity. Three patients with established pancreatic insufficiency have now been evaluated with the oral administration of 30 μCi of [131]-labeled 1,2-Pal-3-IPPA were administered orally with subsequent urine collection for two 24 hour periods. Pancreatic insufficiency was confirmed by the pancreolauryl test and the chemotrypsin level in feces. In the patients with pancreatic insufficiency, substitution of the pancreatic enzymes was discontinued 3 days prior to the investigation. The tracer was administered after an overnight fasting period and a standardized breakfast. Blood samples were drawn after 1,3,4 and 6 hours in 14, 15, 11 and 10 patients, respectively. TLC analysis was performed on the serum lipid extracts with two different solvent systems along with iodobenzoic acid and cold iodinated 1,2-Pal-3IPPA as standards. Solvent system A consisted of petroleum-ether/ether/acetic acid (69:30:1, v/v/v) and solvent system B was composed of benzene/ dioxane/acetic acid (80:18:2, v/v/v). After development of the TLC plates in these solvent systems the standards were again visualized with 254 nm U.V. light and then the plate was cut into 15 segments which were counted. The TLC profiles revealed two major peaks which corresponded to the IBA and tripalmitin standards. The proportion of IBA increased with time. No difference in the count distribution was observed between the two solvent systems. In normals, 76% of the administered activity was excreted in the urine (13.8%) after 24 hours and 98.6% (SD: 14.9%) after 48 hours. The patients with pancreatic insufficiency excreted 26.3% (SD: 15.7%) and 35.9% (SD: 19.1%) of the administered activity, which was significantly decreased (*$p<0.001$) compared to normals.

These combined results show that urine analysis after oral administration of 1,2-Pal-3-IPPA thus appears to be an attractive new technique for the evaluation of pancreatic lipase activity by a simple urine analysis and studies in larger groups of patients with various gastrointestinal diseases are planned.

AGENTS FOR MEDICAL COOPERATIVES

In a continuation of collaborative studies to evaluate the regional uptake in cerebral structures by high resolution autoradiography (ARG), a sample of I-131-labeled "IQNP" was supplied to the Brookhaven National Laboratory (P. Som, D.V.M.). The largest clinical prototype tungsten-188/rhenium-188 generator to date (0.5 Curie) was supplied for clinical studies in a collaborative program with the University of New Jersey School of Medicine and Dentistry (D. M. Goldenberg, M.D., et al.).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

Publications

Fujibayashi, Y., Som, P., Yonekura, Y., Knapp, Jr., F. F., Tamaki, N., Yamamoto, K., Konishi, J. and Yokoyama, A. "Myocardial Accumulation of Iodinated Beta-Methyl-Branched Fatty Acid Analog, [^{125}I](p-Iodophenyl)-3-(R,S)-Methylpentadecanoic Acid (BMIPP), and Correlation to ATP Concentration - II. Studies in Salt-Induced Hypertensive Rats", Nucl. Med. Bio. 20, 163-166 (1993).

Mirzadeh, S. and Knapp, Jr., F. F. "Spontaneous Electrochemical Separation of Carrier-Free Copper-64 and Copper-67 from Zinc Targets," Radiochim. Acta, 57, 193-199 (1992).

Patents

A patent has been issued for the new tungsten-188/rhenium-188 generator system developed in the ORNL Nuclear Medicine Group which provides the carrier-free rhenium-188 radioisotope as perrhenic acid. This new method allows for the use of low specific activity tungsten-188 produced in low flux nuclear reactors and provides concentrated solutions of rhenium-188 for radiolabeling therapeutic agents.

F. F. Knapp, Jr., E. C. Lisic, S. Mirzadeh and A. P. Callahan, "Tungsten-188/Carrier-Free Rhenium-188 Perrhenic Acid Generator System," U.S. Patent No. 5,186,913, issued February 17, 1993.

ORNL Radiopharmaceutical Obtains Approval for Routine Clinical Use

A cardiac imaging agent developed in the ORNL Nuclear Medicine Group by F. F. (Russ) Knapp, Jr., and colleagues has been introduced as a new commercial clinical agent, "Cardiodine™", by Nihon Medi-Physics Co., Inc., following recent approval from the Japanese Food and Drug Administration. Cardiodine™ is the commercial name for iodine-123-labeled BMIPP, which is a structurally-modified fatty acid based on the ORNL concept of "metabolic trapping," which is used to evaluate heart disease. The use of Cardiodine™ permits the unique acquisition of high quality tomographic images to determine the viability of regions of the heart muscle threatened by reduced oxygen availability ("ischemia") resulting from coronary artery disease. These regions of heart muscle can often be "salvaged" or saved from further damage by coronary bypass surgery or balloon angioplasty and are often not detected with the usual radiopharmaceuticals which measure blood flow. Over 600 patient studies were completed with Cardiodine™ in multi-center trials at thirty institutions in Japan which formed the basis for approval of this agent for commercial distribution. Patient studies are also currently in progress at collaborating institutions in Germany and Belgium and are expected to be initiated soon in the Medical Department at Brookhaven National Laboratory.

Proceedings Edited for Generator Symposium

An "Editorial" was recently authored by F. F. Knapp, Jr., S. Mirzadeh and A. P. Callahan, of the ORNL Nuclear Medicine Program, in a special issue of the journal, Radioactivity and Radiochemistry (Vol. 3, No. 4, 1992), which introduced sixteen papers from the "Symposium on Radionuclide Generator Systems for Nuclear Medicine Applications". The symposium was organized by the ORNL researchers at the Annual Meeting of the American Chemical Society (ACS), held in Washington, D.C., on August 24-28, 1992. The symposium encompassed state-of-the-art presentations on radionuclide generator systems for diagnostic and therapeutic applications in nuclear medicine.

International Symposia Features ORNL Radiopharmaceutical for Cardiac Imaging

The Third International Symposium on Radioiodinated Free Fatty Acids for Cardiac

Imaging was recently held in Kyoto, Japan, on February 10-11, 1993, and focussed on the development and clinical applications of the iodine-123-labeled "BMIPP" cardiac imaging agent developed in the ORNL Nuclear Medicine Program by F. F. (Russ) Knapp, Jr., and ORNL co-workers. Knapp was an invited "Keynote Speaker", and also authored several papers at the symposium describing collaborative studies between the ORNL program and other institutions. The Proceedings will be published in the seventeenth Annals of Nuclear Medicine. He also presented an invited lecture on the development and use of radioiodinated free fatty acids for the diagnosis of heart disease at the Seventeenth New Town Conference on Nuclear Cardiology held in Tokyo, Japan, on February 13, 1993.

Researcher Initiates Research Assignment in Australia

Saed Mirzadeh, a staff member in the ORNL Nuclear Group, recently initiated a six-month sabbatical research assignment at the Australian Nuclear Science and Technology Organization (ANSTO) in Lucas Heights, Australia, where he will be involved in collaborative research projects involving the processing of radioisotopes and radionuclide generator systems for nuclear medicine applications. He also presented an invited lecture entitled, "Advances in the Tungsten-188/Rhenium-188 Generator" at the International Symposium on Advances in Radiopharmaceuticals, in Sydney, Australia, on February 5, 1993.

Nuclear Medicine Group Technician Receives Certification

Carla Lambert, a Laboratory Technician in the Nuclear Medicine Group, has recently been certified as a "Laboratory Animal Technician" by the Animal Technician Certification Board of the American Association for Laboratory Animal Science (AALAS). This certification follows six months of preparatory course work, laboratory animal procedure training, laboratory exercises, and successful completion of the Laboratory Animal Technician examination. This is the first AALAS certification to be awarded to a member of the ORNL Health and Safety Research Division and is an important accomplishment consistent with increased emphasis by federal agencies and by the ORNL Animal Care and Use Program on the training and certification of personnel involved with animal studies.

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